EXHIBIT B

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High-Dose Therapy With Stem-Cell Transplantation in the Malignant Lymphomas

ABSTRACT

High-dose therapy with hematopoietic progenitor-cell transplantation plays a key role in the treatment of Hodgkin's disease and the non-Hodgkin's lymphomas. First and foremost, transplantation is used as a salvage treatment for those who relapse or do not achieve a complete remission with first-line chemotherapy. Carefully selected patients with poor prognostic features may benefit from the incorporation of high-dose therapy and transplant into their initial treatment programs. Despite a myriad of trials, many pivotal questions regarding the appropriate application of high-dose therapy with transplantation to the lymphoid malignancies remain unsettled, including the role of allogeneic transplantation and the optimal timing of transplant for patients with poor prognostic indicators. Phase III studies are required to address these issues; these trials will demand the active commitment of concerned transplanters and referring hematologists and oncologists. Although autologous transplantation has been the preferred approach for the majority of patient subgroups, new approaches to allogeneic transplantation that have diminished toxicity may pave the way for a greater role for allogeneic grafting in the lymphoid diseases.

Exquisitely sensitive to chemotherapy or irradiation, malignant lymphomas are characterized by steep dose-response curves that make them prime candidates for the use of dose-intensive therapies. High-dose treatment with hematopoietic progenitor-cell transplantation, therefore, plays a central but ever-changing role in the treatment of these neoplasms.

Therapeutic paradigms for malignant lymphomas continue to evolve. For example, the use of mechlorethamine, Oncovin, procarbazine, and prednisone (MOPP) for the initial treatment of advanced Hodgkin's disease has given way to combinations of MOPP and Adriamycin, bleomycin, and vinblastine, with or without dacarbazine (ABV[D]), and, most recently, to ABVD alone. Changes in the approach to initial treatment, the diminishing morbidity and mortality for high-dose therapy, and the recognition of long-term complications, such as myelodysplasia, have caused experts to continually rethink the optimal role of high-dose therapy with transplantation in the treatment of malignant lymphomas.

The lymphoid malignancies represent a heterogeneous group of diseases; high cure rates with standard regimens are the rule for some patients, while a pattern of repeated relapses is the expected outcome for others. Consistent with the clinical, morphologic, and biological heterogeneity of these diseases, success rates with high-dose therapy plus hematopoietic progenitor-cell transplantation vary.

The establishment of the International Prognostic Index for the non-Hodgkin's lymphomas and a similar panel of clinical prognostic indicators for Hodgkin's disease has helped identify patients destined to be unresponsive to conventional therapies, who may benefit from alternative approaches, including high-dose therapy with hematopoietic progenitor-cell grafting.[1,2] Similarly, many groups have tried to determine parameters that are predictive of outcome with transplantation.[3] These tools help identify subgroups of patients within larger series for whom the expected results of therapy differ.

Disease status is one of the more important prognostic indicators. As a result, patients who respond completely to initial therapy (complete remitters), those who have only a partial response (partial remitters), and those who have primary refractory disease or relapsed disease should be considered separately whenever possible. Given the differences in biological behavior, the individual pathologic entities are best

discussed individually, with subset analysis according to prognostic features when feasible.

Hodgkin's Disease

Relapsed Disease

For patients who suffer a relapse after first achieving a complete remission, the prognosis with conventional salvage therapy is directly related to the duration of the initial remission.[4] The outcome for patients whose remission lasted less than 1 year is dismal with standard-dose second-line treatment, and most experts concur that these patients are best treated with high-dose therapy plus hematopoietic progenitor-cell transplantation. Approximately 40% to 50% of patients with Hodgkin's disease who suffer a relapse within 1 year may be effectively treated with transplantation.[5-10]

For patients whose first remission lasts for more than 1 year, conventional-dose chemotherapy may provide a durable second remission.[4] This is the case regardless of whether the primary therapy was MOPP, ABVD, or MOPP/ABVD. Deaths due to second malignancies and other cumulative toxicities of the treatment limit survival, which ranges from 28% to 47%, depending on the series and length of follow-up.[4,5]

Investigators at Stanford matched patients who underwent high-dose therapy and transplantation for relapsed or refractory Hodgkin's disease to a group of patients with similar characteristics who were treated conventionally.[5] For patients with an initial remission lasting more than 12 months, a statistically significant advantage to transplantation could not be demonstrated. Overall, the most significant predictor of outcome in this analysis was response to cytoreductive therapy.

These findings contrast with results reported by the Vancouver group; their multivariate analysis showed that the length of complete remission was predictive of progression-free survival.[9] Longer follow-up may allow a difference in survival to emerge in the Stanford data.

Neither of the two randomized trials comparing high-dose therapy with autologous transplantation to conventional salvage chemotherapy in patients with relapsed Hodgkin's disease demonstrated a difference in overall survival among patients undergoing transplantation.[11,12] In the first of these studies, Linch and colleagues compared high-dose BEAM (BCNU, etoposide, ara-C, and melphalan) therapy with hematopoietic progenitor-cell transplantation to mini-BEAM salvage therapy in a small number of patients with relapsed or resistant Hodgkin's disease.[11] Accrual was terminated prematurely because patients refused to undergo randomization and, instead, requested high-dose therapy with transplantation. Notably, patients who underwent autologous transplantation had statistically greater event-free and progression-free survival rates. Overall survival rates were the same in the two groups.

A subsequent trial, conducted by the German Hodgkin's Disease Study Group and the European Group for Blood and Marrow Transplantation (EBMT) and reported in abstract form, randomized a larger number of patients with relapsed but chemosensitive disease to receive either additional standard-dose therapy or high-dose therapy with hematopoietic progenitor-cell transplantation.[12] Time to treatment failure was significantly longer with autologous transplantation ($P = .04$), regardless of the interval to relapse, but again, overall survival was not improved.

o **Summary**—Given the apparent preference of patients and physicians for autologous transplantation when conventional therapy has failed, it is extremely difficult to accrue patients to randomized trials. As transplant-related morbidity and mortality decline, an advantage may emerge for the high-dose approach in all patients who relapse, regardless of the duration of remission.

Currently, ABVD is preferred over MOPP or a MOPP-like regimen for the initial treatment of Hodgkin's disease. Although the occurrence of secondary myelodysplasia following transplantation may become less common with the use of the ABVD regimen for first-line treatment, cardiopulmonary complications may occurr more frequently. At present, each patient must be evaluated on an individual basis, and the immediate and long-term risks and benefits of both high-dose therapy with transplantation and salvage chemotherapy must be weighed judiciously.

Refractory Disease

Patients with refractory Hodgkin's disease, unlike those with refractory non-Hodgkin's lymphoma, may achieve durable complete remissions with high-dose therapy and hematopoietic progenitor-cell transplantation.[13-15] Numerous series, including that from the Autologous Blood and Marrow Transplant Registry (ABMTR),[13] demonstrate that high-dose treatment, either chemotherapy alone or combined with radiotherapy, can overcome drug resistance in Hodgkin's disease.

In the ABMTR analysis, patients were considered to have primary refractory Hodgkin's disease if they never achieved a complete remission; evidence of progression on radiologic studies or tissue confirmation of disease was required.[13] Following transplantation, the probability of 3-year progression-free survival was 38%, with an overall survival rate of 50%. Survival following transplant was inversely related to the presence of B-symptoms at diagnosis and Karnofsky performance status (< 90%) at the time of transplant.

Results from the EBMT were similar to those from the ABMTR. The European group reported an actuarial 5-year disease-free survival rate of 30% and an overall survival rate of 34%.[14]

o **Summary**—Overall, patients with refractory Hodgkin's disease benefit from high-dose therapy with progenitor (stem)-cell transplant. Pathologic documentation of residual disease is strongly recommended prior to transplantation, as diagnostic errors are often uncovered when patients do not have the expected response to treatment.

Autologous Transplantation as Part of Initial Therapy

In an attempt to increase overall cure rates for patients with Hodgkin's disease, some centers have begun using autologous transplantation as part of the initial treatment plan for selected patients believed to have a poor prognosis. The results of pilot studies of this approach have been excellent, perhaps reflecting the inclusion of patients with relatively favorable prognoses.[16-19]

Recently, an international effort sought to identify prognostic factors among untreated patients with Hodgkin's disease. This project, which included data on nearly 5,000 patients.

has identified seven key prognostic factors (albumin, hemoglobin, gender, age, stage, leukocytosis, and lymphocytopenia).[2] Patients with three or more of these factors are believed to be at high risk of relapse (with a 5-year freedom from progression rate of 55% to 60%).

This prognostic index will be used to establish eligibility for an intergroup trial that is soon to be launched in the United States. This trial will randomize patients who respond to ABVD induction therapy to either (1) continued conventional-dose treatment or (2) high-dose therapy with hematopoietic progenitor-cell transplantation (Figure 1).

The results of an ongoing European trial comparing autologous transplantation and conventional therapy in responding patients with advanced Hodgkin's disease will also be of interest, although this study is using different prognostic indicators (high lactic dehydrogenase, mediastinal mass > 45%, more than one extranodal site, low hematocrit, and inguinal involvement) to determine eligibility.[20]

Patients with adverse prognostic indicators at the time of diagnosis constitute a small fraction of all patients with Hodgkin's disease, making it even more important that all eligible patients be enrolled in the randomized trials.

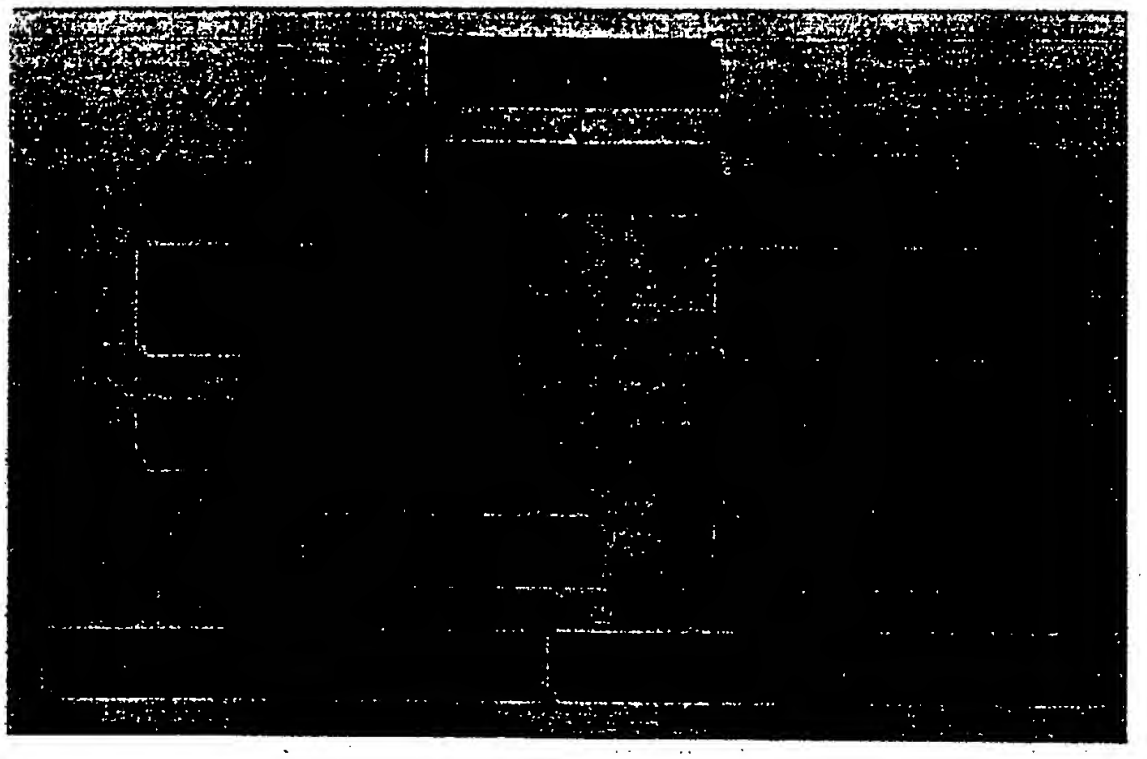

Figure 1: Design of Intergroup Trial for Previously Untreated Patients With Hodgkin's Disease and Poor Prognostic Features

ABVD = Adriamycin, bleomycin, vinblastine, and dacarbazine; HDT/HPCT = high-dose therapy with hematopoietic progenitor-cell transplantation.

Allogeneic Transplantation

Allogeneic transplantation appears to offer little benefit at the cost of great toxicity in the majority of patients with relapsed or refractory Hodgkin's disease.[21-23] Most patients who have undergone allogeneic transplantation have been heavily pretreated.

In the Seattle series, relapse rates were lower in patients treated with allogeneic transplantation than in those who underwent autologous transplantation (45% vs 76% at 5 years; $P = .05$), suggesting the presence of a graft-vs-lymphoma effect.[21] Nonetheless, survival, event-free survival, and mortality due to factors other than relapse did not differ significantly between the two groups.

In the International Bone Marrow Transplant Registry (IBMTR) series, the 3-year probability of relapse was comparatively high (65%), perhaps reflecting the particular patient population selected for allogeneic transplantation.[23] The disease-free survival rate at 3 years was only 15%.

In a case-matched study reported by the EBMT, allogeneic transplantation from a human leukocyte antigen (HLA)–identical sibling donor was also associated with high relapse rates, except in patients with grade 2 or higher acute graft-vs host disease.[22] Although the graft-vs-host reaction appeared to have a suppressive effect on relapse rates, its potential benefits were more than offset by toxicity.

• **Summary**—Allogeneic transplantation seems to be of little benefit in most patients with relapsed or refractory Hodgkin's disease. There remains a small group of individuals with myelodysplasia, however, for whom allogeneic transplantation may be the only alternative. Otherwise, autologous transplantation remains the preferred approach. New approaches to reducing the toxicity associated with allogeneic transplantation and its application earlier in the clinical course may prompt a reconsideration of this recommendation in the future.

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Non-Hodgkin's Lymphoma

The value of high-dose therapy with progenitor-cell transplantation in the non-Hodgkin's lymphomas varies depending on the histologic subtype.

Diffuse, Aggressive Non-Hodgkin's Lymphoma

• **Salvage Therapy**—The role of high-dose therapy with hematopoietic progenitor-cell transplantation in the treatment of patients with chemotherapy-sensitive, diffuse, aggressive non-Hodgkin's lymphoma (intermediate- or high-grade) in relapse has been established by a randomized trial conducted by the Parma group.[24] In this trial, 109 patients who relapsed after having at least a partial response to two courses of salvage therapy were randomly assigned to either high-dose therapy with transplantation or four additional cycles of conventional-dose therapy. Patients on both arms received involved-field irradiation to areas of bulky disease. Notably, all 109 patients had attained a complete remission with first-line therapy.

The event-free survival rate at 5 years was superior in the group who underwent high-dose therapy, compared with the group given standard-dose chemotherapy (46% vs 12%; $P = .001$); the

same was true of 5-year overall survival (53% vs 32%; $P = .038$). Among patients assigned to the conventional arm after the failure of standard-dose salvage treatment, high-dose therapy with transplantation, used as a third-line treatment, was associated with lethal toxicity in the majority of patients (14 of 18). Hence, delaying high-dose therapy until after conventional salvage treatment fails is inadvisable.

Subsequent analysis of this study demonstrated that patients who relapsed early (ie, within 1 year of diagnosis) were less likely to benefit from high-dose therapy than those who experienced a longer remission.[25] Patients with an International Prognostic Index score of 1 to 3, including those with a poor performance status, fared better with high-dose therapy than with standard treatment; thus, poor performance status should not be a reason to exclude patients from high-dose treatment.

Patients with bone marrow involvement were not eligible for the Parma study. However, numerous nonrandomized series that included marrow-positive individuals have shown good outcomes, leading the Lyon Consensus Conference on Intensive Chemotherapy Plus Hematopoietic Stem Cell Transplantation to recommend high-dose therapy with hematopoietic progenitor-cell transplantation for this subgroup of patients if chemosensitivity can be demonstrated.[26]

• **Role of Cytoreduction Prior to Transplantation**—Most centers administer conventional-dose chemotherapy prior to high-dose therapy with transplantation to test the tumor for "chemosensitivity," reduce tumor burden, and "buy time" to obtain approval from the insurer. Numerous retrospective studies suggest that patients who achieve a complete or at least partial remission with conventional-dose chemotherapy have better responses to high-dose therapy than those who have not been tested with standard-dose therapy.

A recent phase III trial provides support for aggressive cytoreduction prior to high-dose therapy with hematopoietic progenitor-cell transplantation.[27] The Groupe d'Etude des Lymphomes de l'Adulte (GELA) randomized patients with refractory or relapsing disease after only a single cycle of salvage chemotherapy to either undergo immediate transplantation or receive two additional cycles of cytoreductive chemotherapy. Although follow-up was short, patients who received additional chemotherapy had a superior event-free survival. Consistent with numerous other reports, patients who were in complete remission at the time of transplant fared better than those who were not. Patients given the more prolonged course of cytoreductive chemotherapy were more likely to achieve a complete remission than those treated with a single course of salvage therapy prior to high-dose therapy with transplantation. However, if a longer course of cytoreductive therapy is administered, the emergence of drug resistance remains a concern.

• **Partial or Slow Responders**—The appropriate approach to patients who achieve less than a complete response or who exhibit a slow response to conventional induction therapy is not yet known. In one small trial, Verdonck et al observed no benefit when patients who achieved only a partial remission after three cycles of CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) chemotherapy proceeded directly to high-dose therapy with transplantation.[28]

A similar trial, also involving a small number of patients, assigned partial remitters to transplantation after they had received only two-thirds of their planned induction treatment.[29] A statistically significant benefit was not demonstrated, although a trend in favor of high-dose therapy was observed.

Since radiologic studies may show residual masses in patients in complete remission, rebiopsy prior to transplantation to document the presence of residual disease is necessary whenever possible. Additional studies are required to explore the optimal treatment strategy for partial or slow responders.

• **Refractory Disease**—Results in patients with truly chemorefractory disease have been poor, leading many centers to consider these patients for alternative investigational therapies.[30,31] Patients with disease that is unresponsive to chemotherapy at the time of relapse have less than a 20% chance of achieving a long-term remission with high-dose therapy with autologous hematopoietic progenitor-cell transplantation.

Analysis of the ABMTR data showed that among 221 patients who had never achieved a complete remission with conventional therapy (primarily induction failures), the only variable predictive of outcome in the multivariate analysis was sensitivity to prior chemotherapy. The 3-year probability of survival was 48% ± 13% for patients with sensitive disease, but only 19% ± 12% for those with unresponsive disease.[31]

Reported series differ in the definition of "refractory" used for the selection of patients. This led the International Consensus Conference on High-Dose Therapy With Hematopoietic Stem-Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas to adopt definitions that hopefully will be used by investigators when designing trials and/or reporting results. The conference members defined refractory disease at the time of relapse as "stable or progressive disease after two cycles of an aggressive salvage regimen." Primary refractory disease was defined as "stable or progressive disease documented at restaging immediately after the completion of induction therapy."[26]

Standardization of the nomenclature should help elucidate whether patients with chemorefractory disease should be offered high-dose therapy with transplantation. The consensus conference found high-dose therapy with hematopoietic progenitor cell transplant to be "inappropriate" in this setting, although this recommendation was based primarily on clinical experience, rather than well-designed clinical trials.[26]

• **High-Dose Therapy as Part of Initial Treatment**—The International Prognostic Index identifies patients with aggressive non-Hodgkin's lymphoma who have a high likelihood of relapse and poor overall survival with conventional first-line therapy.[1] For individuals ≥ 60 years of age, stage, performance status, and lactate dehydrogenase help stratify patients into four subgroups with complete remission rates ranging from 46% to 92% and overall survival rates varying from 32% to 83%.

Many centers have used the International Prognostic Index or other clinical parameters associated with a poor prognosis to select patients for phase II trials incorporating high-dose therapy into the primary treatment plan (Table 1).[32-38] The event-free sur-

Table 1

High-Dose Therapy for Initial Treatment of Advanced Aggressive Non-Hodgkin's Lymphoma With Poor Prognostic Features

Study Group	Number of Patients Randomized	Induction Therapy	Adverse Prognostic Features	Histologic Subtypes	Statistical Difference
GELA[32,33] (LNH87-2)	541	ACVB vs NCVB	ECOG performance status 2-4; ≥ 2 extranodal sites; tumor bulk ≥ 10 cm; bone marrow or CNS involvement; Burkitt's or lymphoblastic histology	Intermediate or high grade	None
	236	ACVB vs NCVB	High-intermediate and high-risk	Intermediate or high grade	$P = .01$ (5-year DFS)
Italian NHL Cooperative Study Group[34]	124	VACOP-B	Bulky stage II (≥ 10 cm); stage III or IV	Diffuse intermediate or high grade (excluding lymphoblastic and Burkitt's histologies)	None
	70	VACOP-B	High-intermediate and high-risk	Diffuse intermediate or high grade (excluding lymphoblastic and Burkitt's histologies)	$P = .008$ (6-year DFS)
Gianni et al[35]	98	MACOP-B vs high-dose sequential therapy	Bulky stage I or II (≥ 10 cm); stage III or IV	Diffuse large cell or diffuse large cell immunoblastic	$P < .001$ (FFP) $P = .004$ (EFS)
GELA[36] (LNH 93-3)	370	ACVB vs intensified induction therapy	High-intermediate and high risk	Intermediate or high grade	$P = .01$[a] (3-year EFS) $P = .003$[a] (3-year survival)
German High Grade Lymphoma Study Group[37]	312	CHOEP	Increased LDH	High grade	None[b]
EORTC[38]	184	CHVmP/Bv	Bulky stage I (≥ 10 cm); stages III or IV[c]	Intermediate or high grade (lymphoblastic lymphoma excluded)	None

[a]Both in favor of standard arm

[b]No survival advantage even when grouped according to International Prognostic Index

[c]68% were in low or low-intermediate risk groups

ACVB = Adriamycin, cyclophosphamide, vindesine, and bleomycin; CHOEP = cyclophosphamide, doxorubicin, Oncovin, etoposide, and prednisone; CHVmP/Bv = cyclophosphamide, doxorubicin, VM-26, and prednisone/bleomycin and vincristine; DFS = disease-free survival; EFS = event-free survival; EORTC = European Organization for Research and Treatment of Cancer; FFP = freedom from progression; GELA = Group d'Etude des Lymphomes de l'Adulte; LDH = lactic dehydrogenase; MACOP-B = methotrexate, Adriamycin, cyclophosphamide, Oncovin, prednisone, and bleomycin; VACOP-B = VePesid, Adriamycin, cyclophosphamide, Oncovin, prednisone, and bleomycin; NCVB = Novantrone, cyclophosphamide, vindesine, and bleomycin.

vival in the reported series has generally been superior to the expected outcome with standard-dose treatment, fueling enthusiasm for this approach. Results of randomized trials have not been uniformly positive, however.

The LNH-87 trial conducted by the GELA demonstrates the importance of using consistent, validated prognostic indicators to select patients for the investigation of "upfront" high-dose therapy with hematopoietic progenitor-cell transplantation.[32] In this study, patients judged to have a poor prognosis by virtue of one or more adverse prognostic factors (Eastern Cooperative Oncology Group [ECOG] performance status of 2 to 4, two or more extranodal

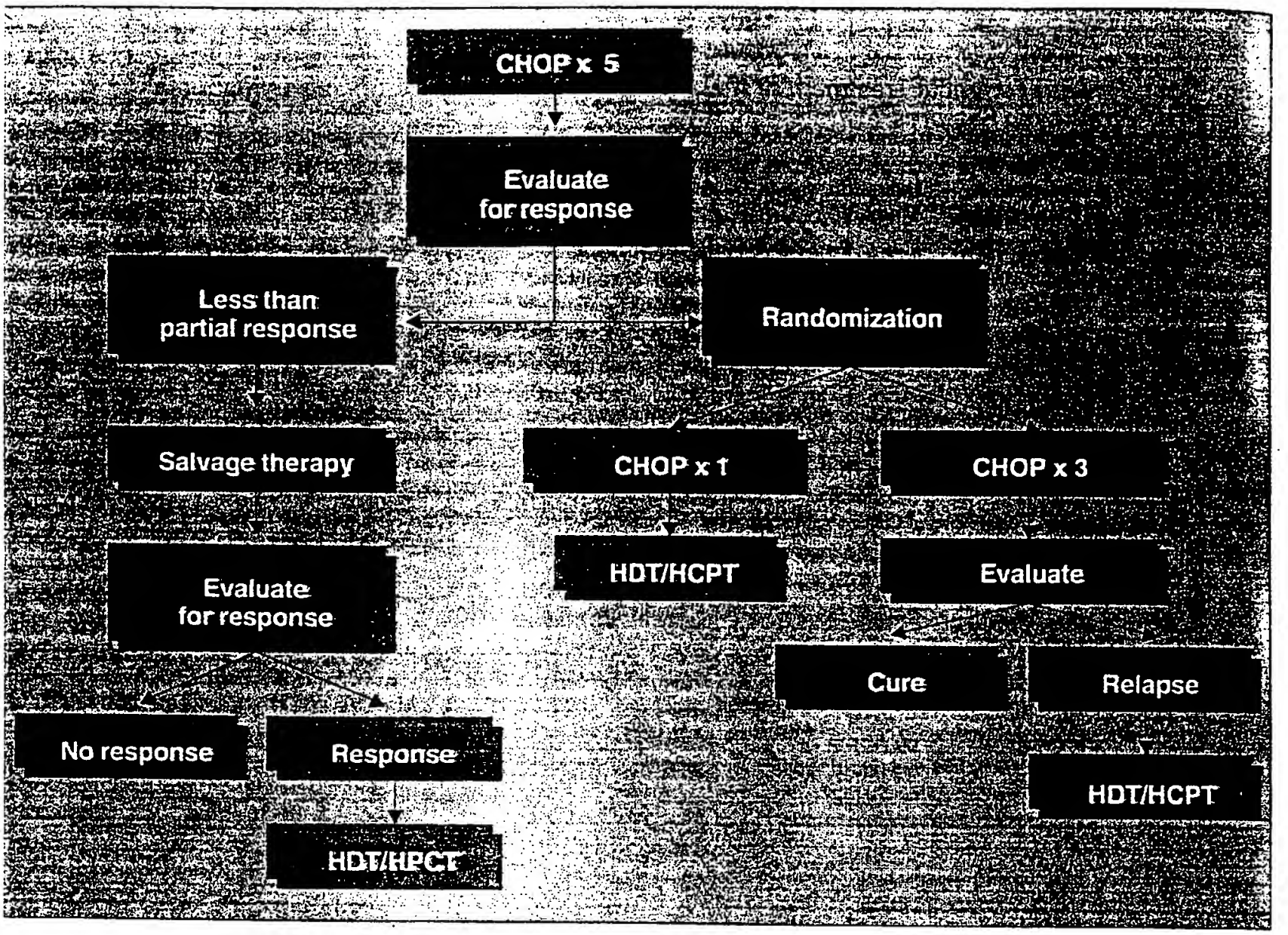

Figure 2: Design of Proposed Intergroup Trial for Patients With High-Intermediate/High-Risk (International Prognostic Index) Diffuse Large Cell Lymphoma

CHOP = cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone; HDT/HPCT = high-dose therapy with hematopoietic progenitor-cell transplantation.

sites, masses greater than 10 cm in diameter, bone marrow or central nervous system involvement, or Burkitt's or lymphoblastic histology) were treated with an anthracycline-containing regimen. Following this treatment, the 541 patients who responded completely were randomized to either additional chemotherapy or autologous transplantation.

The initial analysis of this trial demonstrated no advantage to the more intensive consolidation.[33] Further analysis, which included only the subset of 236 patients who qualified as high-intermediate or high-risk by the more restrictive criteria of the International Prognostic Index, revealed a superior disease-free survival for those undergoing high-dose therapy with hematopoietic progenitor-cell transplantation.

Similarly, the Italian Non-Hodgkin's Lymphoma Study Group trial showed no benefit of high-dose therapy with hematopoietic progenitor-cell transplantation in patients judged to be at high risk of relapse by virtue of tumor bulk or advanced stage disease; however, a striking advantage in disease-free survival was noted when the 70 patients who qualified as high-intermediate or high-risk based on the International Prognostic Index were analyzed.[34] In this subgroup, transplantation yielded a superior 6-year disease-free survival rate (87% vs 48%; $P = .008$), but there was no difference in overall survival. In contrast to the GELA trial, patients in the Italian study were randomized at enrollment, and both responders and nonresponders underwent transplantation.

Patients identified as high risk because of bulky disease or advanced stage by Gianni and colleagues were also randomized at study entry to either conventional therapy or "high-dose sequential therapy."[35] In this series, freedom from disease progression and event-free survival were both superior in patients receiving high-dose therapy with hematopoietic progenitor-cell transplantation—findings that are consistent with the results of both the GELA LNH-87 study and the Italian Study Group trial.

None of the aforementioned studies demonstrated a statistically significant prolongation of survival with early transplantation, possibly because of the benefit from salvage high-dose therapy with hematopoietic progenitor-cell transplantation among patients in the conventional-dose arm who relapsed.

The duration and dose-intensity of induction therapy may influence the impact of high-dose therapy with trans-

plantation on outcome. In an attempt to increase the percentage of patients achieving a complete remission with induction therapy and ultimately survival, the GELA compared standard induction with a dose-intensive, three-cycle regimen prior to transplantation in the LNH 93-3 trial.[36] No improvements in either the remission or survival rate were seen. Two additional randomized studies designed to investigate the role of transplantation in poor-prognosis patients after short-course conventional-dose induction therapy showed no benefit to high-dose therapy with hematopoietic progenitor-cell transplantation.[37,38]

• **Summary**—Additional studies are in progress throughout the world, and results should be reported soon. In the United States, an intergroup trial to address the issue of high-dose therapy with transplantation for poor-prognosis patients, particularly its timing, has been planned (Figure 2). Given the conflicting data, accrual to phase III randomized trials is imperative. Use of the International Prognostic Index for the selection of patients will facilitate interpretation of the data by limiting enrollment to individuals who are at high risk of relapse with conventional chemotherapy.

Low-Grade Non-Hodgkin's Lymphoma

Given the anticipated lengthy survival for patients with low-grade non-Hodgkin's lymphoma, most of the experience with transplantation has been in patients experiencing a second or subsequent remission or those in relapse, thus avoiding the potential for morbidity and mortality in newly diagnosed patients.[39-43] Although response rates are high, a continuing pattern of relapse has been observed with autologous transplantation, much like that associated with conventional-dose treatment.

Some experts have suggested that high-dose therapy, although not curative, changes the natural history of the disease by providing durable remissions and delaying relapse. In the most recent update from Nebraska, consisting of 174 patients with relapsed or refractory disease, the actuarial event-free survival rate at 6 years was 36% and the overall survival rate at 6 years was 61%.[41] In a multivariate analysis, independent predictors of a poor outcome included more than two prior chemotherapy regimens, the presence of resistant disease, and the presence of follicular large cell lymphoma.[41] A continuous pattern of relapse was observed.

A similar trial from England demonstrated a higher rate of freedom from progression but not an improvement in overall survival in individuals who underwent autologous transplantation, as compared with historical controls.[43] In the Dana-Farber series of patients with a sensitive relapse or partial first remission, the median time to relapse was only 13 months, but the overall survival rate at 12 years from diagnosis was 70%, which is longer than is usually reported for newly diagnosed patients.[39]

• **Summary**—The benefits ascribed to transplantation are difficult to prove in the absence of a randomized trial, particularly in view of the fact that transplanted patients represent a highly selected subpopulation.

Mantle Cell Lymphoma

Known for its unremitting clinical course when treated conventionally, mantle cell lymphoma also has proven relatively resistant to high-dose treatment, especially when used as salvage therapy.[44,45] Although remissions are achievable, relapse is the rule when autologous transplantation is used to treat recurrent or refractory disease. Relatively few patients with mantle cell lymphoma have undergone allogeneic transplantation. The reported results of this transplant approach vary and follow-up is short.[46]

Incorporating high-dose therapy into the initial overall treatment plan may be more likely to provide durable remissions. At M. D. Anderson, the results of using an intensive induction regimen followed by autologous or allogeneic transplantation have been encouraging.[47] Among previously untreated patients, the event-free survival rate at 3 years was 72%, as compared with a 17% rate in previously treated individuals. Although two of eight patients undergoing allogeneic transplantation died due to chronic extensive graft-vs-host disease, both were in remission at the time. Also, none of the allogeneic transplant patients have relapsed, despite the poor prognostic features of this group, including prior extensive treatment and lack of response to induction therapy.

• **Summary**—Larger trials will be needed to determine the appropriate role of allogeneic transplantation in the treatment of mantle cell lymphoma and to better assess the existence of a graft-vs-lymphoma effect.

High-Grade Lymphomas

Burkitt's lymphoma, Burkitt-like lymphomas, and lymphoblastic lymphoma are all eminently curable in most children. However, these high-grade non-Hodgkin's lymphomas are associated with relatively poor long-term survival rates in adults, despite significant improvements in outcome due to the application of more effective intensive regimens, such as those used in the pediatric population.

Most large transplantation series include a small percentage of patients with small, non-cleaved or lymphoblastic lymphomas in relapse or second remission, with varying results. Autologous transplantation during first remission has been investigated in an attempt to improve disease-free survival in patients who are sufficiently chemosensitive to attain a complete response to induction treatment.

Data from the EBMT registry (EBMTR) provide the largest series of patients with these pathologic subtypes.[48,49] According to these data, disease status at the time of transplant is the most important predictor of outcome in adult patients with high-grade non-Hodgkin's lymphoma. For Burkitt's and Burkitt-like lymphomas, the 3-year actuarial overall survival rate was 72% for patients transplanted during first complete remission, compared with 37% in those with a chemosensitive relapse and 7% in patients with disease that was unresponsive to chemotherapy. For patients with lymphoblastic lymphoma, the 6-year actuarial survival rate ranged from 63% in patients who were in first complete remission to 15% in those who had resistant disease. Patients in second complete remission had an intermediate survival rate of 31% at 6 years.

• **Summary**—Since these statistics represent registry data, the criteria for selecting patients for transplantation are unknown and are likely to have varied among centers. The results with transplantation appear to be superior to conventional-dose salvage chemotherapy.

However, the role of transplantation during first remission is unclear. This issue needs to be explored further in carefully designed clinical trials in which established criteria for identification of patients with poor prognoses governs patient eligibility for transplantation.

Autologous Graft Purging

The role of purging of the autologous graft in the non-Hodgkin's lymphomas remains to be established. At the Dana-Farber Cancer Institute, transplantation during first remission of follicular lymphoma was associated with an especially favorable outcome in patients whose purged autologous grafts showed no evidence of residual lymphoma when studied by the polymerase chain reaction (PCR).[50] Purging with a cocktail of anti–B-cell antibodies appeared to favorably affect outcome by reducing the time to relapse, but not survival.

Other researchers have argued that antibody purging and the achievement of a "clean" marrow was not responsible for the durable remissions, but rather, that a negative PCR result is a marker of low disease bulk and better prognosis. Data from the EBMTR showed no difference in progression-free or overall survival when purged and unpurged non-Hodgkin's lymphoma cases were compared; however, there was an inexplicable increase in overall survival associated with purging when the low-grade lymphoma cases were analyzed separately.[51]

• **Summary**—Although some series have established an association between a negative PCR assay and durable remissions, most authorities concur that the majority of relapses are likely to derive from residual disease in the patient, rather than from small numbers of malignant cells contaminating the autologous graft. Randomized trials comparing purged and unpurged autologous grafts would be optimal but are unlikely to be conducted. Gene marking studies that distinguish malignant cells deriving from the autologous graft from those that remain in the patient following chemotherapy may shed light on this issue.

Allogeneic Transplantation

Allogeneic transplantation has the advantage of providing a graft that is free of contaminating malignant cells; it may also suppress the lymphoma through a possible graft-vs-lymphoma effect. Most reports of allogeneic transplantation for the non-Hodgkin's lymphomas describe small groups of patients who vary widely with regard to histologic subtype and prior therapy. Clearly, some very high-risk patients may be cured. Moreover, responses to donor lymphocyte infusions among those who relapse following transplantation support the existence of a graft-vs-lymphoma effect.

The EBMT reported the outcomes of 764 allogeneic bone marrow transplants for lymphoma, including 113 patients with low-grade, 272 with intermediate/high-grade, and 222 with lymphoblastic lymphomas.[52] Among these patients, 104 had Hodgkin's disease. The progression-free survival rates at 4 years were 42% for low-grade lymphoma, 48% for intermediate/high-grade lymphoma, 38% for lymphoblastic lymphoma, and 44% for Burkitt's lymphoma. The overall survival rates at 4 years for the same subgroups were 50%, 50%, 42%, and 39%, respectively. The results of allogeneic grafting in patients with Hodgkin's disease were especially poor, yielding a 20% progression-free survival rate and a 25% overall survival rate at 4 years.

Nearly 10,000 patients who underwent autologous transplants were compared to the allogeneic transplant group in a multivariate analysis. Allogeneic transplantation produced a lower relapse rate than autologous transplantation for low-grade lymphoma ($P = .0005$) and intermediate/high-grade lymphoma ($P = .0006$). The reverse was true for Hodgkin's disease. With regard to overall survival, autologous transplantation was superior to allogeneic grafting in all groups, with the exception of patients with Burkitt's lymphoma, in whom there was no difference between the two types of transplant.

Similar results have been reported by the IBMTR in 113 patients with low-grade lymphomas.[53] Progression-free and overall survival rates at 3 years were both 49%. Allogeneic transplantation appears to be associated with a plateau on the survival curve of patients with low-grade non-Hodgkin's lymphoma, suggesting that a subset of patients may be cured.

• **Summary**—Improvements in supportive care or approaches that minimize toxicity while harnessing the graft-vs-lymphoma response (eg, mini-transplants)[54] may improve outcomes in patients with lymphoma who undergo allogeneic transplantation.

At present, allogeneic transplantation can be recommended only for young patients with low-grade lymphoma and HLA-matched donors or for those from whom a suitable autologous graft cannot be collected.

Stem-Cell Source

Throughout the world, peripheral-blood progenitor cells have virtually replaced the traditional bone marrow autologous graft. Ease of collection, rapidity of engraftment, and a possible reduction in the degree of malignant contamination have been the reasons for this shift in stem-cell source over the past decade.

In Hodgkin's disease but not in non-Hodgkin's lymphomas, a case-control study performed by the EBMT demonstrated a surprisingly higher relapse rate with the use of mobilized peripheral-blood progenitor cells.[55] Whereas Hodgkin's disease tends to recur at sites of prior disease and not at distant locations or in bone marrow, it is difficult to explain the results of this EBMT study.

To further investigate the effect of stem-cell source on outcome in Hodgkin's disease, investigators at University College in London matched patients from their institution who received a uniform preparative regimen and either a peripheral blood stem-cell transplant or a conventional autologous bone marrow transplant.[56] Patients were matched for factors previously shown to have prognostic significance in patients undergoing autologous transplantation at University College. Neither overall survival nor progression-free survival differed between the groups.

Preliminary results from a randomized trial at the University of Nebraska also suggest that stem-cell source does not affect outcome in non-Hodgkin's lymphoma.[57]

• **Summary**—The available data suggest that peripheral blood progenitor cells and bone marrow are associated with similar relapse rates in the non-Hodgkin's lymphomas. The data on Hodgkin's disease are mixed, but the biology of the disease argues against

stem-cell source being a significant issue in transplantation.

Late Complications

Treatment-associated myelodysplasia and acute leukemia, as well as solid tumors, occur in patients following autologous high-dose therapy with hematopoietic progenitor-cell transplantation for lymphoid malignancies.[58] Late complications likely relate to the conventional-dose therapy administered prior to transplantation, with a contributing role played by the high-dose regimen.

The cumulative incidence of myelodysplasia or acute leukemia may be as high as 14% to 18% at 5 to 7 years, the period during which patients are at greatest risk.[59-61] Solid tumors and non-Hodgkin's lymphomas related to prior therapy occur less commonly, but the period of risk is more prolonged.[58,61,62] Patient age, the duration of prior therapy, and the particular agents administered appear to predict treatment-related complications. The use of peripheral blood progenitor cells rather than bone marrow has been associated with secondary malignancies for unclear reasons.[61,62]

Cytogenetic analysis may link the complication to particular agents (eg, abnormalities of chromosomes 5 and 7 to prior alkylator therapy).[60] Pretransplant cytogenetic evaluation or analysis for the presence of clonal hematopoiesis may identify patients at risk, prompting the physician to seek an alternative stem-cell source or therapy.[63,64]

The high cumulative frequency of late complications in patients with lymphoid malignancies undergoing high-dose therapy with transplantation may tip the risk-benefit balance against transplantation in some situations (eg, during first remission). Also, alterations in the conventional-dose primary therapy, such as the change from MOPP to ABVD, may have a significant impact on the frequency of late complications. Continued vigilance will be required in this changing environment.

Future Directions

As this review demonstrates, many questions remain regarding the optimal use of high-dose therapy with hematopoietic progenitor-cell transplantation in the malignant lymphomas. The collaborative approach, in which clinical trials groups join forces to answer important questions that require hundreds and sometimes thousands of patients, is most likely to provide timely answers to these questions.

Prognostic indices for both non-Hodgkin's lymphoma and Hodgkin's disease now provide criteria for patient selection according to a risk assessment that is accepted internationally and based on hard data derived from large patient numbers.[1,2]

Clinicians should keep in mind that the goal of therapy for the lymphomas is long-term survival with a high quality of life. Thus, as therapeutic paradigms shift, we must continue to monitor patients for the long-term consequences of our therapies.

While it is important to ask the "big" questions in phase III trials, some of the biggest advances come from innovative studies at single institutions involving only a handful of patients. The introduction of cellular therapies, such as ex vivo activated T-cells or vaccines, as adjuncts to high-dose therapy with transplantation for the lymphoid malignancies, holds great promise for improving outcomes.[65] The incorporation of targeted therapies, such as radioimmunoconjugates, into high-dose therapy approaches may also improve disease-free and overall survival through the elimination of drug-resistant disease.[66] Nonmyeloablative allogeneic transplantation, in which toxicity is minimized but the graft-vs-lymphoma effect is retained, may extend the benefits of allogeneic transplantation to a larger and older pool of patients with lymphoid malignancies.[54]

These are exciting times in the management of malignant lymphomas. Strategic use of resources in support of both large clinical trials and translational studies and a continued collaborative spirit are likely to yield big dividends for patients and investigators as we enter the next millennium.

This article is reviewed on pages 1645, 1646, and 1653.

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The Writer Article Reviewed

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Approximately 35,000 stem (progenitor)-cell transplants are performed annually worldwide, with an estimated yearly growth rate of between 10% and 20%.[1] Non-Hodgkin's lymphoma remains the second most common indication for stem-cell transplantation, and Hodgkin's disease ranks approximately seventh overall.[1]

Despite these statistics, there remains significant controversy regarding such issues as the timing of transplantation, source of stem cells, and the need for post-transplant therapy. Winter carefully and thoroughly reviews the role of stem-cell transplantation in the Hodgkin's and non-Hodgkin's lymphomas.

Hodgkin's Disease

With respect to patients with Hodgkin's disease, we agree completely with Winter that high-dose therapy plus autologous hematopoietic progenitor-cell transplantation is indicated for the majority of patients who relapse. We would go one step further and assert that most, if not all, relapsed patients should be considered for transplantation, regardless of the duration of first remission. Like Winter, we would also advocate high-dose therapy for patients with primary refractory disease.

Hopefully, the issue of how to integrate high-dose therapy into the initial treatment of untreated, "high-risk" patients will be resolved by the current intergroup trial (outlined in Winter's Figure 1). A recent German trial, however, did not demonstrate any advantage to dose escalation of the BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin, procarbazine, and prednisone) regimen over standard doses of BEACOPP.[2]

The issue of the development of secondary myelodysplasia in patients following high-dose therapy remains problematic and merits careful consideration before proceeding with this therapy. However, we agree with Winter and others[3] that the treatment given prior to high-dose therapy likely precipitates the development of myelodysplastic syndrome following high-dose therapy. This risk should decline as first-line therapy becomes safer.

Despite the apparent benefits of high-dose therapy in patients with relapsed Hodgkin's disease, the majority of these patients will suffer additional recurrences. Therefore, we must continue to improve first-line therapies, investigate additional treatments (eg, radiation, immune therapies) that can be delivered after high-dose therapy, and explore the use of allogeneic grafts.

Non-Hodgkin's Lymphomas

Providing a general statement on the utility of high-dose therapy in non-Hodgkin's lymphomas is more problematic because of the inherent complexity and diversity of the diseases that fall under this heading. The evidence clearly supports a role for high-dose therapy in patients with relapsed, chemosensitive, aggressive non-Hodgkin's lymphomas, and argue against its use in patients with chemorefractory disease. Data on the use of high-dose therapy in patients with partial responses and in untreated patients with high-risk features remain unclear and controversial, however.

We agree with Winter's comprehensive review of the role of high-dose therapy in the various clinical settings and non-Hodgkin's lymphoma histolo-

gies. Our comments will focus on several issues: (1) the role of high-dose therapy as part of initial therapy; (2) the source of the stem cells utilized; and (3) the use of adjuvant therapy concurrently with or following high-dose therapy to maximize its benefit.

• **High-Dose Therapy as Part of Initial Therapy**—The International Prognostic Index (IPI) demonstrates that, in patients with more than one of the age-adjusted risk factors (elevated lactic dehydrogenase level, stage, and performance status), long-term disease-free survival is affected by both a low complete remission rate and a high recurrence rate in the complete remitters. We believe that both of these issues need to be addressed in the design of novel chemotherapeutic approaches. The positive results reported by Gianni and colleagues using high-dose sequential therapy support this hypothesis.[4] This program integrated high-dose therapy with intensive pretransplant therapy.

Our confirmatory phase II, pilot trial of high-dose sequential therapy in the United States duplicated Gianni's superior results with a similar program.[5] However, a phase III study comparing this approach to standard CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) therapy could not be completed because of poor patient accrual. We feel that it is essential that the oncology community address this issue and support ongoing clinical trials investigating the role of high-dose therapy as part of initial therapy (see Winter's Figure 2).

• **Source of Stem Cells**—The selection of stem cells—allogeneic vs autologous, peripheral blood vs bone marrow, and purged vs unpurged—hinges on two important, incompletely resolved issues: (1) the frequency and importance of clonogenic tumor cells in the graft; and (2) the role that the graft-vs-lymphoma effect may play in the treatment of these diseases. In general, we agree with Winter's review of these important questions and look forward to clinical trials designed to address them. Of particular interest will be the use of nonablative allogeneic transplantation and/or posttransplant immunomodulatory treatments to uncouple the deleterious effects of graft-vs-host disease from the beneficial aspects of the graft-vs-lymphoma response.

• **Role of Adjuvant Therapy**—Finally, the role of adjuvant therapy following transplantation has not been clarified, due to the lack of randomized studies comparing the different therapies. Data from our group and others suggest the possible value of radiation therapy to sites of prior bulk disease following high-dose therapy.[Boyle T, Morr J, Water D, et al, unpublished data, 1999] However, phase III trials will be needed to document the efficacy of this approach over standard therapy.

Similarly, numerous agents (eg, antibodies, interferons, and interleukins) have shown promising results when used posttransplantation. However, without the rigors of randomized, controlled studies, these agents cannot be considered as part of standard therapy at present.

Summary

In summary, we agree with Winter that "these are exciting times" in the management of patients with lymphomas. Data indicating that high-dose therapy improves the chances of curing patients with Hodgkin's disease and non-Hodgkin's lymphoma justify the position of the latter disease as the second most common indication for autologous high-dose therapy. Despite the advances that have been made, however, a great deal more needs to be accomplished via the integration of basic science into carefully controlled clinical trials so that the majority of patients undergoing high-dose therapy are ultimately cured of their disease.

—Alice Hwang, MD
—David P. Schenkein, MD

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The Writer Writes Renewed

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The number of new cases of Hodgkin's disease and non-Hodgkin's lymphoma diagnosed and treated each year are increasing. Although human immunodeficiency virus (HIV) infection and toxins in the environment and workplace may be responsible for the development of these diseases in some patients, explanations for this increase remain elusive. Lymphoid malignancies continue to be among the most responsive to chemotherapy and radiation therapy, however, and a sizeable percentage of affected patients are cured after primary therapy.

For Hodgkin's disease, newer, more

The Winter Article Reviewed

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Autologous hematopoietic stem-cell transplantation has become an accepted therapy for some patients with Hodgkin's disease and non-Hodgkin's lymphoma. Convincing evidence for a graft-vs-lymphoma effect has led to increasing use of allogeneic transplantation in these patients. Dr. Winter has written an excellent overview of transplantation in the lymphomas. She has focused on several areas of controversy and described results of randomized trials.

Physicians who perform transplants are continually faced with decisions about the suitability of patients for autologous hematopoietic stem-cell transplantation, as well as the timing of the procedure. These decisions cannot be made without standardized definitions that allow us to interpret the literature.

Dr. Winter discusses the difficulties in defining "primary refractory" disease. This issue was also addressed at the International Consensus Conference on Hematopoietic Stem-Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas.[1]

Philip et al noted no long-term disease-free survivors after autologous hematopoietic stem-cell transplantation in patients with primary refractory disease.[2] These patients had failed to attain a complete remission and had disease progression while receiving salvage chemotherapy. However, the terms "primary refractory" and "induction failure" have also been used to describe patients who attain a partial remission or a "very good partial remission" with primary therapy. These patients are not *refractory* and may have an excellent prognosis following autologous hematopoietic stem-cell transplantation.[3,4]

Early Transplantation in Poor-Prognosis Patients

Dr. Winter also discusses the role of early transplantation as part of primary therapy for poor-prognosis non-Hodgkin's lymphoma patients. One example of a poor prognosis is a slow response to initial chemotherapy.[5] Two prospective randomized trials have addressed the use of autologous hematopoietic stem-cell transplantation to improve results in these slow responders. The first trial randomized patients in partial remission after three cycles of CHOP (cyclophosphamide, Adriamycin, Oncovin, and prednisone) to receive either autologous hematopoietic stem-cell transplantation after one more cycle of CHOP or five more cycles of CHOP.[6] The second trial randomized patients who were in partial remission two-thirds of the way through primary therapy to recieve treatment with either autologous hematopoietic stem-cell transplantation or six cycles of DHAP (dexamethasone, cytarabine, and Platinol) salvage therapy.[7]

Neither trial showed a survival benefit of autologous hematopoietic stem-cell transplantation, although the results of these trials should not necessarily be interpreted to mean that slow responders do not have a poor prognosis or that autologous hematopoietic stem-cell transplantation cannot improve outcome for these patients. These trials seem to suggest that a single course of high-dose therapy followed by autologous hematopoietic stem-cell transplantation can substitute for a certain number of cycles of CHOP or similar conventional chemotherapy. It may be unreasonable to expect a single course of high-dose therapy to benefit patients who have a significant residual tumor burden after receiving a partial course of their initial conventional chemotherapy regimen.

Although these trials did not show a benefit of autologous hematopoietic stem-cell transplantation when used *at the time of slow response*, it is possible that autologous hematopoietic stem-cell transplantation might be beneficial at a later time. This hypothesis could be tested by a clinical trial that randomizes slowing responding patients to receive either additional conventional chemotherapy alone or additional chemotherapy followed by high-dose therapy and autologous hematopoietic stem-cell transplantation.

Incorporating Transplantation Into Primary Therapy

Dr. Winter also discusses the conflicting results of trials that have incorporated autologous hematopoietic stem-cell transplantation into primary therapy, including the Groupe d'Etude des Lymphomes de l' Adulte (GELA) LNH93-3 trial.[8] Poor-prognosis patients in this trial were initially treated with a brief induction chemotherapy regimen and then were randomized to either additional conventional chemotherapy or high-dose therapy followed by autologous hematopoietic stem-cell transplantation.

Again, the failure of autologous hematopoietic stem-cell transplantation to improve outcome in this trial may be attributed to the fact that transplantation was utilized too early in the course of disease, before significant cytoreduction was obtained. Interestingly, the international consensus committee also recognized that the only trials that showed a benefit of early autologous hematopoietic stem-cell transplantation in poor-prognosis non-Hodgkin's lymphoma patients were those that employed a full course of standard induction therapy prior to autologous stem-cell transplantation or those that incorporated high-dose therapy into the initial induction regimen.[1]

The randomized trials of early autologous hematopoietic stem-cell transplantation for poor-prognosis non-Hodgkin's lymphoma seem to indicate that there is a narrow window of applicability if patients are to benefit from this approach. Transplantation cannot be used too early (before sufficient cytoreduction is obtained with conventional therapy), and it appears that autologous hematopoietic stem-cell transplantation is only likely to benefit patients with adverse prognostic characteristics. The role of early autologous hematopoietic stem-cell transplantation can be refined if we enroll patients in trials like the intergroup study described by Dr. Winter.